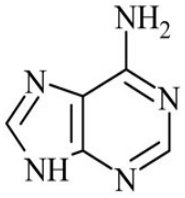
Nucleotide metabolism

Pyrimidine and purine are the names of the parent compounds of two types of nitrogen-containing heterocyclic aromatic compounds. Adenine and guanine are the principal purines of both DNA and RNA. Caffeine (coffee) and theobromine (cocoa) are naturally occurring purines. Pyrimidines that occur in DNA are cytosine and thymine. Cytosine and uracil are the pyrimidines in RNA. Nucleoside is a structure formed by the combination of nitrogen base and sugar whereas Nucleotides are phosphoric acid esters of nucleosides.



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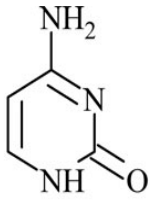

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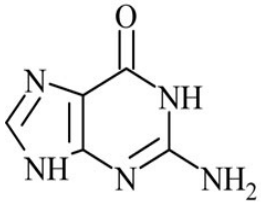

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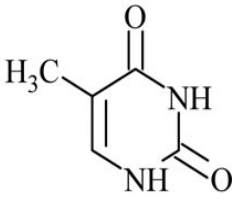


T

Nucleotide synthesis

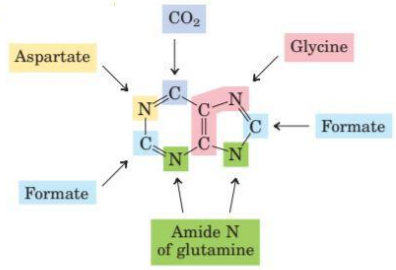
The biosynthesis of nucleotides can be via *de novo* pathway or salvage pathway. In *de novo* pathway, nucleotide bases are assembled from simpler compounds. The framework for a pyrimidine base is assembled first and then attached to ribose. Whereas, the framework for purine base is synthesized piece by piece directly onto a ribose-based structure.

In salvage pathway, preformed bases are recovered and reconnected to a ribose unit. Both pathways lead to synthesis of ribonucleotides. All deoxyribonucleotides are synthesized from corresponding ribonucleotides. The deoxyribose sugar is generated by reduction of ribose within a fully formed nucleotide. The methyl group that distinguishes the thymine of DNA from uracil of RNA is added at the last step in the pathway.

***De novo* pathway**

Purine ribonucleotide

The purine ring is assembled from variety of precursors: glutamine, glycine, aspartate, N^{10}-formyltetrahydrofolate and CO_2.



Origin of the ring atoms of purines. This information was obtained from isotopic experiments with ^{14}C- or ^{15}N-labeled precursors. Formate is supplied in the form of N^{10}-formyltetrahydrofolate.

1. In the first committed step of the pathway, an amino group donated by glutamine is attached at C-1 of PRPP. The resulting 5-phosphoribosylamine is highly unstable, with a half-life of 30 seconds at pH 7.5. The purine ring is subsequently built up on this structure.

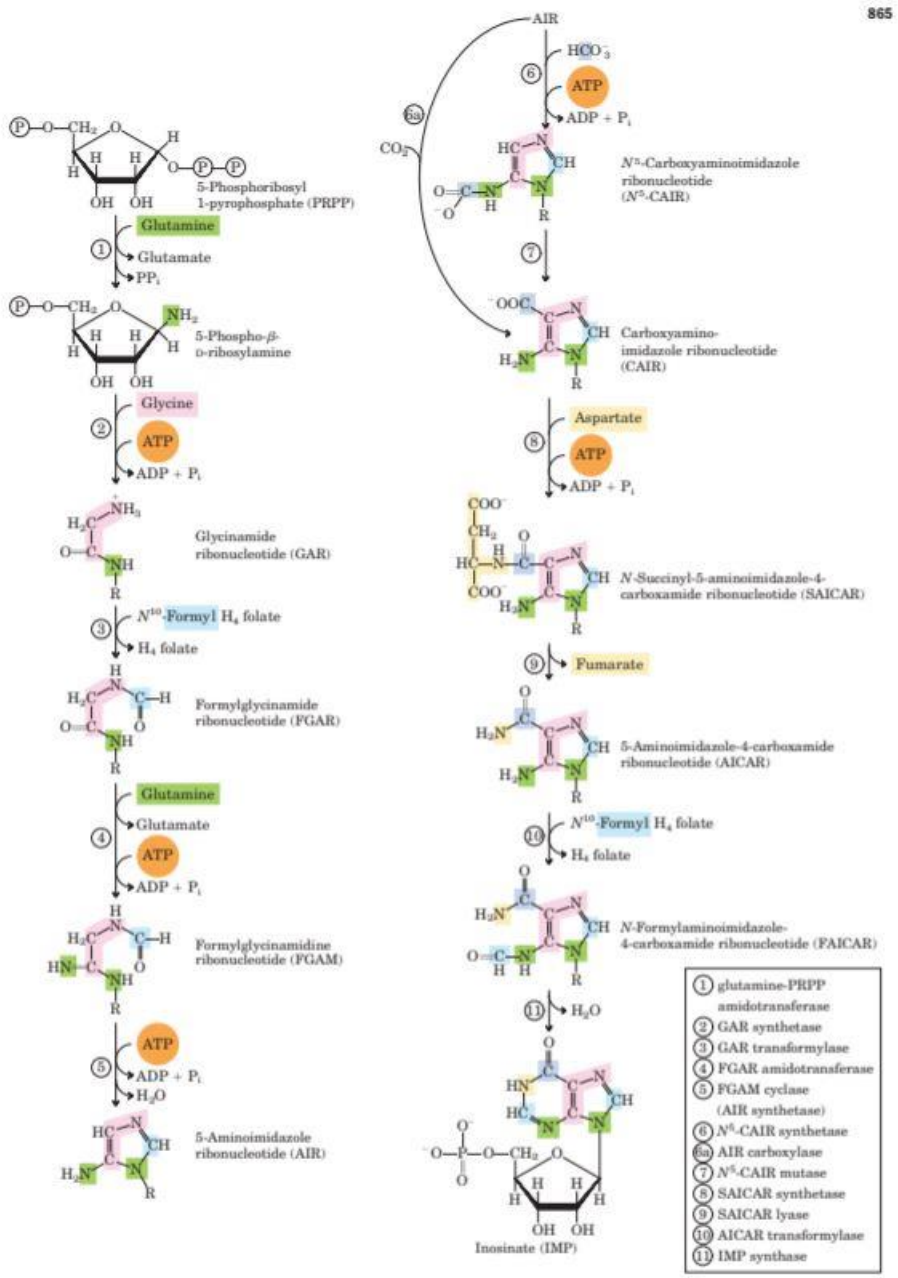
The pathway described here is identical in all organisms, with the exception of one step that differs in higher eukaryotes as noted below.

2. The second step is the addition of three atoms from glycine. An ATP is consumed to activate the glycine carboxyl group (in the form of an acyl phosphate) for this condensation reaction.
3. The added glycine amino group is then formylated by N^{10}- formyltetrahydrofolate.
4. A nitrogen is contributed by glutamine.
5. Dehydration and ring closure yield the five-membered imidazole ring of the purine nucleus, as 5-aminoimidazole ribonucleotide. At this point, three of the six atoms needed for the second ring in the purine structure are in place.
6. To complete the process, a carboxyl group is first added. This carboxylation is unusual in that it does not require biotin, but instead uses the bicarbonate generally present in aqueous solutions.
7. A rearrangement transfers the carboxylate from the exocyclic amino group to position 4 of the imidazole ring.

Steps 6 and 7 are found only in bacteria and fungi. In higher eukaryotes, including humans, the 5-aminoimidazole ribonucleotide product of step 5 is carboxylated

directly to carboxyaminoimidazole ribonucleotide in one step instead of two (step 6a). The enzyme catalyzing this reaction is AIR carboxylase.

8. Aspartate now donates its amino group by formation of an amide bond
9. This is followed by elimination of the carbon skeleton of aspartate (as fumarate).
10. The final carbon is contributed by N^{10}-formyltetrahydrofolate
11. A second ring closure takes place to yield the second fused ring of the purine nucleus.



Purine synthesis by *de novo* pathway

AMP and GMP are formed from IMP

The conversion of IMP to either AMP or GMP utilizes a two-step, energy-requiring pathway. Note that synthesis of AMP requires GTP as energy source, whereas the synthesis of GMP requires ATP.

AMP: adenosine 5'-monophosphate

GMP: guanosine 5'-monophosphate

IMP: inosinate

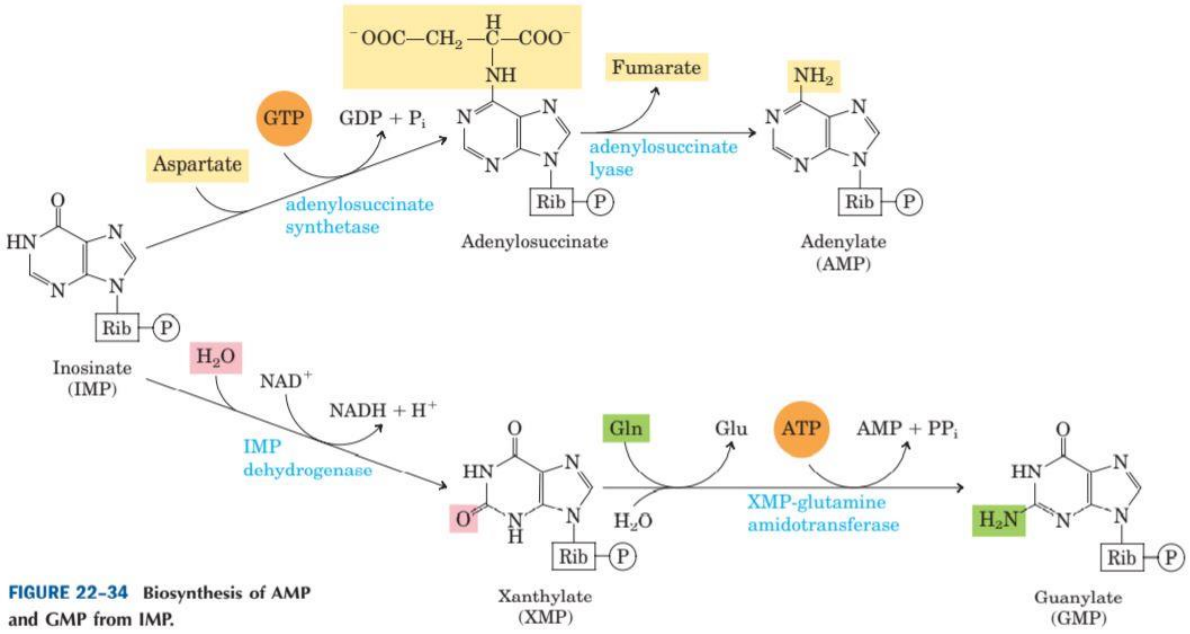


FIGURE 22-34 Biosynthesis of AMP and GMP from IMP.

Purine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition

Three major feedback mechanisms cooperate in regulating the overall rate of *de novo* purine nucleotide synthesis and the relative rates of formation of the two end products, adenylate and guanylate.

1. The first mechanism is exerted on the first reaction that is unique to purine synthesis transfer of an amino group to PRPP to form 5-phosphoribosylamine. This reaction is catalyzed by the allosteric enzyme glutamine-PRPP amidotransferase, which is inhibited by the end products IMP, AMP, and GMP.

AMP and GMP act synergistically in this concerted inhibition. Thus, whenever either AMP or GMP accumulates to excess, the first step in its biosynthesis from PRPP is partially inhibited.

2. In the second control mechanism, exerted at a later stage, an excess of GMP in the cell inhibits formation of xanthylate from inosinate by IMP dehydrogenase, without affecting the formation of AMP. Conversely, an accumulation of adenylate inhibits formation of adenylosuccinate by adenylosuccinate synthetase, without affecting the biosynthesis of GMP.
3. In the third mechanism, GTP is required in the conversion of IMP to AMP, whereas ATP is required for conversion of IMP to GMP, a reciprocal arrangement that tends to balance the synthesis of the two ribonucleotides. The final control mechanism is the inhibition of PRPP synthesis by the allosteric regulation of ribose phosphate pyrophosphokinase. This enzyme is inhibited by ADP and GDP, in addition to metabolites from other pathways of which PRPP is a starting point.

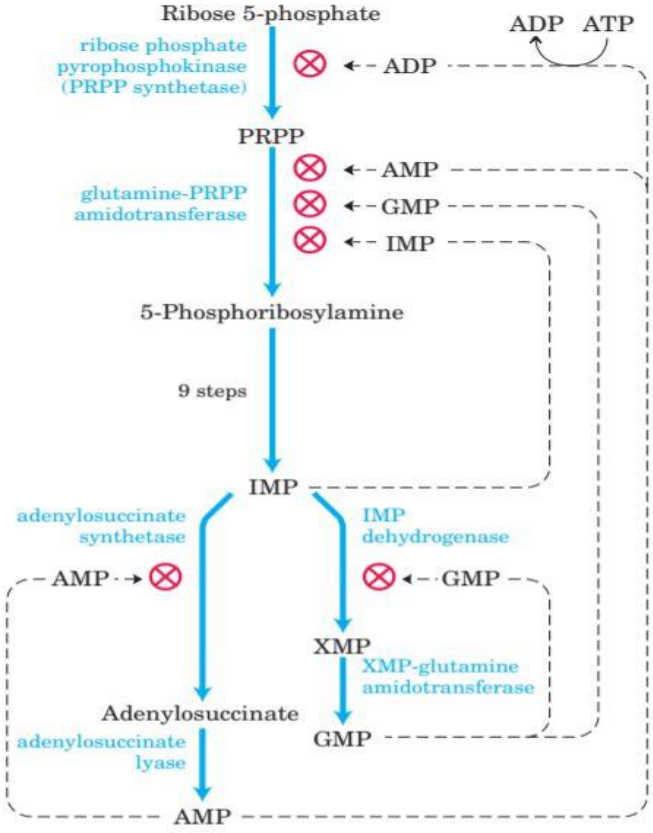


FIGURE 22–35 **Regulatory mechanisms in the biosynthesis of adenine and guanine nucleotides in *E. coli*.** Regulation of these pathways differs in other organisms.